BRCA and beyond: The contribution of genetics to breast and gynecologic cancers (Part 2)

By Kate McReynolds, APRN, MSc, MSN, ANP-BC, AGN-BC

To participate in this CE program, click *here*[A].

Faculty

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Intended audience

This continuing education (CE) activity has been designed to meet the educational needs of nurse practitioners who provide care for women in any age bracket.

CE approval period

Now through November 30, 2018

Estimated time to complete this activity

1 hour

CE approval hours

1.0 contact hour of CE credit

Needs assessment

This two-part article focuses on hereditary cancer syndromes associated with breast and gynecologic cancers. In part 1, the author provided background information about hereditary cancer, detailed several specific hereditary breast and gynecologic cancer syndromes (HBGCSs), and explained the gene alterations involved in these syndromes. In part 2, the author describes ways that healthcare providers can identify women who may have one of the two most common syndromes and who could therefore benefit from genetic risk assessment, counseling, and testing—processes she also discusses. The author also explains how to interpret genetic test results and provides management recommendations for the two most common HBGCSs.

Educational objectives

At the conclusion of this educational activity, participants should be able to:

1. Know how to identify women without or with a personal history of cancer who may have hereditary breast and ovarian cancer (HBOC) syndrome or Lynch syndrome (LS) and who could benefit from genetic risk assessment, counseling, and testing.
2. Describe how to interpret genetic test results.
3. Delineate management recommendations for women with HBOC syndrome or LS.

Accreditation statement

This activity has been evaluated and approved by the Continuing Education Approval Program of the National Association of Nurse Practitioners in Women's Health (NPWH), and has been approved for 1.0 contact hour of CE credit.

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This two-part article focuses on hereditary cancer syndromes associated with breast and gynecologic cancers. In Part 1 of this article[B], the author provided background information about hereditary cancer, detailed several specific hereditary breast and gynecologic cancer syndromes (HBGCSs), and explained the gene alterations involved in these syndromes. In Part 2, the author describes ways that healthcare providers can identify women who may have one of these syndromes and who could therefore benefit from genetic risk assessment, counseling, and testing—processes she also discusses. The author explains how to interpret genetic test results and provides management recommendations for the two most common HBGCSs.

KEY WORDS: **hereditary breast and gynecologic cancer syndrome, hereditary breast and ovarian cancer, HBOC, *BRCA1*, *BRCA2*, Lynch syndrome, genetic testing**

In the course of their practice, healthcare providers (HCPs) may encounter women—some with no personal history of cancer and some with such a history—who have a hereditary breast and gynecologic cancer syndrome (HBGCS) but are not aware of it.[1] If these women are identified, screening and/or risk-reduction measures can be implemented with the goal of preventing new cancers from developing or finding new cancers at an early stage. In addition, relatives of women found to have an HBGCS can be offered individualized, quantified assessment of their own cancer risk, as well as options for tailored screening and prevention strategies.[2] In this article, readers will learn more about identifying women who may have hereditary breast and ovarian cancer (HBOC) syndrome or Lynch syndrome (LS), the two most common HBGCSs; the genetic risk assessment, counseling, and testing processes; and management recommendations for HBOC syndrome and LS.

Genetic risk assessment

Taking a personal and family history is key in determining whether a woman is a candidate for genetic risk assessment for HBOC syndrome or LS.

HBOC syndrome

For women *without* a personal history of cancer, the National Comprehensive Cancer Network's (NCCN's) clinical practice guidelines for genetic/familial high-risk assessment for HBOC syndrome[C] suggest further genetic risk evaluation in those meeting *any* of the following criteria[3]:

- Having a close blood relative (i.e., a first-, second-, or third-degree relative) with a known mutation in a cancer susceptibility gene within the family, two or more breast cancer primaries, ovarian cancer, or male breast cancer; or having two or more relatives on the same side of the family with breast cancer primaries, with at least one of them diagnosed at age 50 or younger (early onset)
- Having a first- or second-degree relative with breast cancer at age 45 or younger
- Having a family history of three or more of the following (especially if early onset and can include multiple primaries in the same individual): breast, pancreatic, or

prostate cancer (Gleason score ≥7 or metastatic); melanoma; sarcoma; adrenocortical carcinoma; brain tumors; leukemia; diffuse gastric cancer; colon, endometrial, thyroid, or kidney cancer; dermatologic manifestations (e.g., trichilemmoma) and/or macrocephaly; hamartomatous polyps of the gastrointestinal (GI) tract

To evaluate these women, HCPs can use one of several brief familial risk stratification tools listed in the U.S. Preventive Services Task Force (USPSTF) **recommendation statement**[D].[4] The USPSTF found insufficient evidence to recommend one tool over another but stated that the Breast Cancer Genetics Referral Screening Tool and the FHS-7 are the simplest and fastest to administer. All of the tools have a checklist and a threshold score that should prompt a referral for genetic counseling. In general, the more red flags discovered through use of a tool, the greater the likelihood that an HBGCS is present. Of note: If a patient reports that a relative has had ovarian or uterine cancer, HCPs should make sure that the diagnosis was either of these cancers and not cervical cancer. Also of note and importance: *Because family history is dynamic, HCPs should assess all patients for changes in this history on a regular basis—for example, at the annual visit.*

For women *with* a personal history of cancer, the aforementioned NCCN guidelines suggest further genetic risk evaluation in those meeting any of these criteria[3]:

- A woman with ovarian cancer
- A woman with a breast cancer diagnosis and any of the following: a known mutation in a cancer susceptibility gene within the family; early-onset breast cancer; triple-negative breast cancer diagnosed at age 60 or younger; two breast cancer primaries; a male relative with breast cancer; and/or breast cancer at any age and any of the following:
  - at least one close blood relative with early-onset breast cancer
  - at least one close blood relative with invasive ovarian cancer at any age
  - at least two close blood relatives with breast cancer, prostate cancer (Gleason score ≥7 or metastatic), and/or pancreatic cancer at any age
  - pancreatic cancer at any age
  - being from a population at increased risk
- An Ashkenazi Jew with breast, ovarian, or pancreatic cancer at any age
- A woman with a personal or family history of three or more of the following (especially if early onset and can include multiple primary cancers in the same individual): breast, pancreatic, or prostate cancer (Gleason score ≥7 or metastatic); melanoma; sarcoma; adrenocortical carcinoma; brain tumors; leukemia; diffuse gastric, colon, endometrial, thyroid, or kidney cancer; dermatologic manifestations (e.g., trichilemmoma) and/or macrocephaly; hamartomatous polyps of the GI tract

Lynch syndrome

According to NCCN's **clinical practice guidelines for genetic/familial high-risk assessment for hereditary colorectal cancer**[E], a woman who has a personal or family history of an LS-related cancer (colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, brain [usually glioblastoma], or small intestinal cancer; sebaceous adenoma or carcinoma; or keratoacanthomas as seen in Muir-Torre syndrome) should undergo an evaluation to exclude LS if she has any of the following[5]:

- A known LS mutation in the family
- Colorectal cancer (CRC) or endometrial cancer diagnosed before age 50
- CRC or endometrial cancer and another synchronous or metachronous LS-related cancer
- CRC or endometrial cancer and at least one first- or second-degree relative with LS-related cancer diagnosed before age 50
- CRC or endometrial cancer and at least two first- or second-degree relatives with LS-related cancers, regardless of age
- CRC or endometrial cancer at any age with tumor showing evidence of mismatch repair (MMR) deficiency, either by microsatellite instability or loss of MMR protein expression
- A family history of at least one first-degree relative with CRC or endometrial cancer diagnosed before age 50
- A family history of at least one first-degree relative with CRC or endometrial cancer and another synchronous or metachronous LS-related cancer
- A family history of at least two first- or second-degree relatives with LS-related cancer, including one diagnosed before age 50
- A family history of at least three first- or second-degree relatives with LS-related cancers, regardless of age
- An LS-related cancer or being unaffected but with at least a 5% risk of having an MMR gene mutation based on predictive models

Genetic counseling

If, on the basis of a woman's personal and/or family history and a focused physical examination, an HCP suspects that she may have a genetic predisposition to cancer, she can be referred for genetic

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counseling provided by a clinician with training and expertise in cancer genetics. Pre-test genetic counseling includes the following[1,3,6,7]:

- Collection of a comprehensive family history, which includes information about first-, second-, and third-degree relatives on both sides of the family;
- Generation of a differential diagnosis and education about the cancer risks and screening/risk-reducing recommendations associated with that syndrome;
- Education about the genetics of cancer and inheritance patterns, including the risk of passing on a genetic mutation to children;
- Discussion about the specific test(s) that may be ordered and the technical accuracy of the test(s);
- Education about the possible outcomes of testing: positive, negative, or a variant of uncertain significance (VUS);
- Review of the medical implications of a positive, negative, or VUS test result, including the possibility that a test result might not be useful in making healthcare decisions;
- Discussion about the psychological risks and benefits of learning one's genetic test result;
- Review of the legal implications of testing, including the Genetic Information Nondiscrimination Act, and potential cost implications of testing; and
- Obtaining informed consent for testing (written informed consent is strongly recommended).

Post-test genetic counseling involves results disclosure, discussion of medical management, implications for family members, and discussion of psychosocial impact, especially if a mutation has been identified.[1]

Genetic testing and interpretation

In the past, genetic testing entailed testing for one gene/syndrome at a time, which was costly. Recent advances in genome sequencing technologies have resulted in a substantial reduction in the cost of genetic testing and the ability to test for many different genes/syndromes at the same time using multi-gene panels.[8]

Laboratories classify DNA sequence variants identified during testing into 5 categories: benign, likely benign, VUS, likely pathogenic, or pathogenic. With regard to clinical implications, the first two categories are considered negative results, and VUS means that it is unclear whether the variant detected in the gene increases cancer risk or is a benign finding. Relatives should not be tested nor clinical decisions made on the basis of a VUS result. By contrast, the last two categories are considered positive results (i.e., they indicate that a mutation is present) that should prompt consideration of genetic testing in the patient's relatives as well.[9]

If a likely pathogenic or pathogenic variant, say, in *BRCA1*, has already been identified in a given family member—for example, in a 52-year-old mother—and her daughter undergoes genetic testing, there are only *two possibilities* in terms of the daughter's test result: It is either (1) positive: she has the mutation; clinical decisions regarding surveillance and risk-reducing surgery need to be made; and *her* first-degree relatives, who have a 50/50 chance of having the *BRCA1* mutation themselves, can be tested; or (2) negative: she does not have the mutation, she has no chance of passing down the mutation to a child, and she is not at increased genetic risk for the cancers associated with the *BRCA1* mutation for which her mother is at risk.

However, if no specific likely pathogenic or pathogenic variant has been identified in a given family as yet, and a member of that family undergoes genetic testing (based on her family history and/or clinical presentation), then there are *three possible results*: (1) positive (see #1 in the previous paragraph); (2) negative, but with limitations; and (3) VUS. To elaborate on #2—that is, if the results are negative when no familial mutation has been identified—there are *four possible scenarios*: (a) The results are truly negative: Despite all the red flags, all of the cancer in the family is sporadic; (b) There *is* a genetic mutation present, but it cannot be detected by the laboratory's technology; (c) There *is* a genetic mutation present, but it was not tested for; or (d) There *is* a genetic mutation in the family, but the person who was tested did not inherit it. To decrease the likelihood of this last scenario occurring, *a fam-*

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ily member with cancer should be tested first, if possible.

It is conceivable that, in a given family, two family members could have cancer wherein one tests positive for the familial gene mutation and the other tests negative. For example, there may be a *BRCA1* mutation in a family in which two sisters are diagnosed with premenopausal breast cancer. One sister may test positive for the mutation, whereas the other may have developed a sporadic cancer.

Management recommendations

Various management strategies are available for women who test positive for a gene mutation associated with an HBGCS. The particular options recommended depend on the syndrome identified and the woman's needs and preferences. In this section, NCCN's current management recommendations for HBOC syndrome and LS are summarized; those for Li-Fraumeni syndrome and Cowden syndrome, two other HBGCSs, are available here[C] and those for Peutz-Jeghers syndrome, another HBGCS, are available here[E].

HBOC syndrome

Main management options for women with a *BRCA1/2* mutation are increased surveillance, risk-reducing surgery, and chemoprevention.[3] A pharmacotherapeutic approach for advanced cancer and psychotherapy for the emotional sequelae of risk-reducing surgical therapies are also discussed.

Enhanced surveillance

Options include annual magnetic resonance imaging (MRI) of the breast starting at age 25; annual breast MRI and mammography starting at age 30; and clinical breast examinations every 6-12 months, starting at age 25.

Surgery

Options include risk-reducing bilateral mastectomy (RRBM) and risk-reducing salpingo-oophorectomy (RRSO). RRSO is typically performed at age 35-40, upon completion of childbearing, but may be delayed until age 40-45 in women with a *BRCA2* mutation (ovarian cancer onset occurs an average of 8-10 years later in women with a *BRCA2* mutation than in those with a *BRCA1* mutation). For women who elect RRSO, the role of concomitant risk-reducing hysterectomy (RRH) is controversial. A 2016 prospective study of more than 1,000 women with a *BRCA1/2* mutation who underwent RRSO without RRH showed that 8 incident endometrial cancers occurred (4.3 were expected in this population).[10] Although overall risk for endometrial cancer after RRSO was not increased, the risk for serous/serous-like endometrial carcinoma was increased in *BRCA1*-positive women. These findings were not replicated in a 2017 prospective study of 828 women with a *BRCA1/2* mutation in which 5 incident endometrial cancers occurred (2.04 were expected in this population).[11] None of these cancers were serous/serous-like; all were of the endometrioid subtype. Of note, 4 of the 5 women were obese (body mass index >30 kg/m^2) and 3 of the 5 had taken tamoxifen after a breast cancer diagnosis. Both obesity and tamoxifen exposure are known risk factors for endometrial cancer.[12] Current management guidelines for women with a *BRCA1/2* mutation do not recommend RRH.

Women who do not elect RRSO should know that screening for ovarian cancer through transvaginal ultrasound (TVUS) and/or serum CA-125 measurement has not been found to be sufficiently sensitive or specific to warrant recommendation but can be considered.[3] Growing evidence suggests that the Fallopian tube epithelia may be the main etiologic site for development of high-grade serous carcinoma, the most common and aggressive serotype of epithelial ovarian cancer.[13] As a consequence, salpingectomy alone—albeit not currently recommended by the NCCN[3]—is emerging as a possible prophylactic option; clinical trials are ongoing.

Chemoprevention

Few data are available with respect to the efficacy of the selective estrogen receptor modulator (SERM) tamoxifen in reducing breast cancer risk in *BRCA1/2* mutation carriers who have not undergone RRBM. However, limited retrospective data suggest a possible benefit.[14] Earlier research suggested that tamoxifen may be effective in premenopausal women with a *BRCA2* mutation but not in those with a *BRCA1* muta-

tion.[15] This finding may be related to the fact that women with a *BRCA1* mutation are more likely to develop triple-negative breast cancer.[16] The SERM raloxifene and the aromatase inhibitors exemestane and anastrozole have been shown to reduce breast cancer risk in postmenopausal women, but no data on their use in women with a *BRCA1/2* mutation are available.[3,14,17]

Pharmacotherapy

For women with advanced ovarian cancer who are *BRCA1/2* positive and have been treated with three or more prior lines of chemotherapy, an additional pharmacotherapeutic option is available. Based on results of a 2015 international multicenter, single-arm trial of 137 patients, the FDA approved the use of olaparib, a poly (ADP-ribose) polymerase (PARP) inhibitor.[18] An FDA-approved companion diagnostic *BRCA1/2* test is available.[19] Results of this test are used as an aid in identifying ovarian cancer patients with deleterious or suspected deleterious germline *BRCA* variants eligible for treatment with olaparib. Ongoing studies are evaluating the efficacy of olaparib for metastatic breast cancer in women with a germline *BRCA* mutation.[20]

Counseling

In addition to these management strategies, HCPs need to address the psychosocial and quality-of-life effects of RRBM and/or RRSO. According to the results of a study presented at the 2014 annual meeting of the American Society of Clinical Oncology, most *BRCA1/2* carriers experience sexual dysfunction, menopausal symptoms, cognitive stress problems, and poor sleep following RRSO.[21] A blogger describes how she felt 6 weeks post-RRBM in **Me and My Foobs: What It's Really Like Post-Mastectomy**[F].[22] The genetic testing process itself, not to mention learning of a pathogenic mutation or a VUS result, can lead to substantial distress.[23] Counseling can be considered to address some or all of these adverse effects.

Lynch syndrome

Management options for women with an *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM* mutation include increased surveillance, risk-reducing surgery, and chemoprevention.[5]

Surveillance

To reduce the risk for developing CRC, patients in whom one of the aforementioned gene mutations is identified should undergo colonoscopy starting at age 20-25, with the test repeated every 1-2 years. Colonoscopy should be performed 2-5 years prior to the earliest CRC in the family if a relative was diagnosed with the disease before age 25.

Endometrial cancer screening may be considered in women with LS who have not undergone RRH, but it does not have proven benefit. Some women may choose to undergo endometrial biopsy every 1-2 years. TVUS can be considered in postmenopausal women, but it is not recommended in premenopausal women because of the wide range in endometrial stripe thickness throughout the normal menstrual cycle. Women should be educated about signs and symptoms (S/S) of endometrial cancer, including any abnormal uterine bleeding. S/S should be reported promptly and evaluated with endometrial biopsy.

No effective screening for ovarian cancer exists; women who have not undergone RRSO need to be educated about S/S that may indicate disease: bloating, early satiety, difficulty eating, pelvic or abdominal pain, increased abdominal girth, and urinary frequency or urgency. If these S/S persist and are a change from a woman's baseline status, they should be evaluated promptly. Serum CA125 and TVUS may be considered at the HCP's discretion. Screening guidelines for other cancers associated with LS can be found **here**[E].[5]

Surgery

If adenomatous colon polyps are identified and cannot be resected during colonoscopy, or if high-grade dysplasia is noted, then segmented or extended colectomy is recommended. The remaining colonic mucosa should be scoped every 1-2 years.

Women with LS who have completed childbearing are advised to consider RRH and RRSO. RRH has been shown to reduce the incidence of endometrial cancer, but not endometrial cancer mortality. RRSO may reduce the incidence of ovarian cancer. The decision about whether to undergo RRH/RRSO and the timing of surgery should be individualized and take into account the patient's family history, co-morbidities, and menopause status; the gene with the mutation (endometrial and ovarian cancer risks vary, depending on the mutated gene); and whether childbearing is complete.

Chemoprevention

Data suggest that aspirin may decrease CRC risk, but the optimal dosage and duration of treatment have not been established. A recent observational study showed that hormonal contraceptive (HC) use was associated with a lower risk for endometrial cancer.[24] However, prospective data are needed before HCs can be recommended to reduce the risk for gynecologic cancers in women with LS.

Conclusion

Identifying and managing an HBGCS begins by taking a good family history, and not just one time.

HCPs need to be familiar with all the red flags suggesting that such a syndrome may be present and make referrals to a clinician with expertise in cancer genetics as indicated. Many genes are associated with HBGCSs, and more will be discovered over time. Finally, HCPs also need to keep in mind that, unless a woman is being tested for a gene mutation already known to exist in her family, a negative result does not necessarily mean that she is not at increased risk for an HBGCS.

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